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~~Description~~

Parenteral pharmaceutical compositions containing ammoniumalkyl salts of 2-arylpropionic acids.

The object of the present invention consists of pharmaceutical compositions suitable for parenteral administration which contain alkylammonium salts of 2-arylpropionic acids.

In particular, although the parenteral pharmaceutical compositions of the invention are suitable to be obtained with any 2-arylpropionic acid having antiinflammatory activity, they preferably contain, as 2-arylpropionic acid, ketoprofen or 3-benzoyl-α-methylbenzeneacetic acid, ibuprofen or 2-(4-isobutylphenyl)propionic acid, naproxen or (S)-6-methoxy-α-methyl-naphthaleneacetic acid and tiaprofenic acid or 5-benzoyl-α-methyl-2-thiopheneacetic acid, the ketoprofen being the 2-arylpropionic acid particularly preferred.

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One of the advantages ~~represented by~~ of the pharmaceutical compositions of the invention is that it allows for the administration of the non-steroid antiinflammatory substance by a route of administration, the parenteral one, which does not show side effects as shown by the pharmaceutical forms administered by topical route such as, for example, creams, lotions, gels or ointments which, because of their easy methods of application, are widely used. It is in fact known from literature on the subject that topical administration of non-steroid anti-inflammatory drugs can, in a more or less serious manner, provoke damage to the patient's skin due to

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the ~~fotolability~~ photolability of the drug which, in the presence of light, undergoes a degradation process, the products of which interfere negatively on the cellular membrane by the formation of free radicals.

The pharmaceutical compositions of the invention represent, moreover, a notable improvement as far as stability and convenience of use and safety are concerned with respect to the compositions already on the market containing the same anti-inflammatory drugs.

A decisively more advantageous aspect of said pharmaceutical compositions is that their administration causes uneasiness ~~but tolerable, with respect to~~ which is tolerable, compared to the pain, sometimes intense, caused by the compositions for parenteral use on the market containing the same anti-inflammatory drugs.

In particular, as far as ketoprofen is concerned, the ~~relative smallness of the~~ relatively small side effects and the recognised effectiveness in the symptomatic treatment of rheumatoid arthritis, in osteoarthritis, in anchylosing spondylitis, of acute painful articular and periarticular symptoms of the musculoskeletal system, in gout and in dysmenorrhea, in the treatment of pain and inflammation which accompanies or follows orthopaedic operations, have made ~~of~~ such a drug one of the most frequently used active principles ~~of largest use~~ in oral administration among anti-inflammatory non-steroid drugs of current therapeutical use.

The analgesic and anti-inflammatory effect of ketoprofen has been, in a large measure, correlated to its capacity, or more specifically, to the capacity of

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its S-enantiomer, ~~of inhibiting the~~ to inhibit the synthesis of prostaglandin ~~synthesis~~. More recently, it has been recognised that the R-enantiomer, which in human beings does not undergo an appreciable metabolic conversion in the S-antipode, has its own analgesic property, mediated by ~~mechanism~~ mechanisms of action which, even though not fully clarified, seem to be completely independent from the prostaglandin synthesis block.

Pharmaceutical formulations for parenteral use containing as active principle ketoprofen and/or its enantiomers are thought to be particularly useful in the treatment of acute exacerbations of painful manifestations and as adjuvant in the symptomatic therapy of pain in persons suffering from terminal cancer, in individual therapeutic treatment ~~as~~ and in association with muscle relaxants, pain-killers and central analgesics.

The 2-arylpropionic acids with anti-inflammatory activity of the present invention are made up of highly lipophilic carboxylic acids and as such are scarcely soluble in water. Nonetheless it is possible to prepare solutions of said acids, after salification in aqueous vehicles containing a surplus of a hydrate, of a bicarbonate and/or of an alkaline carbonate or an earth alkaline carbonate such as, for example, sodium hydroxide, sodium bicarbonate, of a preferably basic

α-aminoacid or of a hydroxyalkylamine, eventually in the presence of preservatives and excipients and/or dispersing agents.

Said solutions of the 2-arylpropionic acids present a



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gradual instability easily evidenced from a progressive yellowing, sometimes followed by turbidity and by separation of floccules, phenomena which become more noticeable with ~~the~~ a temperature ~~'s~~ increase and after ~~the solution's~~ a prolonged exposure of the solution to ~~the~~ light. To overcome said difficulty, recourse was made to lyophilized pharmaceutical formulations from which the injectable solution is reconstituted just at the moment of use by means of solubilization in the proper solvent. These solutions contain, furthermore, variable quantities of preserving substances among which ~~are mainly used the~~ the most frequently used are p-hydroxybenzoate of methyl and propyl, and supporting materials in excess such as, for example, glycine, to ensure the volume and compactness of the lyophilized substance itself. The use, together with the active principles, of a ponderal excess of supporting materials ~~imply~~ results in that the constituted solutions present pH values which vary from 6.5 to 7.3 and are definitely ~~result~~ hypertonic. In fact, the osmolarity values ~~are~~ measured ~~covering~~ cover an interval from 650 to 1150 mOsm/kg, which ~~are~~ is not very compatible with the isotonicity of biological fluids, which present values comprised between 275 and 295 mOsm/kg. As a result, the administration of such solutions causes pain to the patient and, moreover, superficial liquid effusions can come about. The presence of remarkable quantities of excipients and of the preserving agents in the solution can moreover be the cause of risks deriving from the patient's individual susceptibility to said substances.

It is known that, on the English market, formulations

have long been introduced for ~~the extemporary~~ extemporaneous use consisting of a ketoprofen solution in a mainly aqueous medium containing an excess of l-arginine, benzylic alcohol and citric acid; said solutions, which present a global pH of about 6.7, are supplied in dark glass containers for a better control of their stability.

The pharmaceutical compositions suitable for parenteral use ~~object~~ of the present invention, are made up of aqueous solutions of alkylammonium salt of 2-arylpropionic acids chosen from the group consisting of ketoprofen, ibuprofen, naproxen and tiaprofenic acid in racemic or in enantiomeric form, which present osmolarity values comprised in the range 270-310 mOsm/kg and pH values comprised in the range 7.0-7.5.

As alkylammonium bases, ~~are utilised~~ bases which include alkyl radicals eventually substituted with hydroxy radicals are used. In the case ~~that~~ where the alkylammonium base exists in a racemic or enantiomeric form, the salts can comprise either one or the other of said forms. Bases particularly preferred are α-aminoacids such as lysine and particularly preferred is the salt formed with the forms of said aminoacid having the natural configuration. Another preferred base is the dropropizine or 3-(4-phenyl-1-piperazinyl)-1,2-propanediols. The salifying acid is preferably employed in its racemic form even though salts formed from its separate enantiomers are comprised within the scope of the invention.

The particularly preferred salts are those of (R,S)-ketoprofen with d,l-lysine and with l-lysine

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respectively described in US 4,279,926 (21.07.81) and BE 882.889 (14.05.80). Other salts, ~~as~~ for example the R- or S-ketoprofen salts with the separated stereoisomers of lysine and dropropizine, are also known and have been described in WO 94/20449 (15.09.94).

According to the process of the invention, the pharmaceutical compositions suitable for parenteral use containing salts of a 2-arylpropionic acid selected from the group consisting of ketoprofen, ibuprofen, naproxen and tiaprofenic acid with alkylammonium bases are prepared by solubilizing in an inert-gas atmosphere and away from light, in an aqueous solution, at a pH ranging from 7.0 and 7.5, the alkylammonium salt of the chosen 2-arylpropionic acid.

The use of an inert gas during the preparation of the solutions and their subsequent conservation ~~allows the~~ enable reaching ~~of such~~ a degree of stability sufficient ~~so as~~ to avoid a recourse to the use of preservatives and co-solvents such as, for example, alcohols or glycols for preventing the progressive yellowing of the solutions. Inert gases particularly preferred are those which are chemically inert with solvents and solutes and are compatible with the foreseen pharmaceutical use: these are, as example, nitrogen and the rare gases helium and argon and their mixtures.

Besides ~~to grant~~ granting the composition of the invention a good tolerability, the lack of benzyl alcohol or other solvent, except water for injectable preparations, also gives the consumer a precise information about

the quality of the composition itself. In fact, should the pharmaceutical composition undergo alterations due to an incorrect storage, the ~~appearing~~ appearance of a characteristic whitish opalescence indicates these alterations immediately and therefore the pharmaceutical composition will be not administered. The appearance of said opalescence, ~~representing~~ which represents a very sensitive index of the pharmaceutical quality of the active principle contained in the composition of the invention, is a guarantee of the quality of the composition, and furthermore, it represents a noticeable improvement ~~in~~ with respect to those compositions which contain co-solvent agents, such as in particular benzyl alcohol, and consequently do not make evident the possible presence of alterations which would ~~cause~~ render the pharmaceutical quality of the composition ~~not anymore~~ no longer acceptable.

The packaging, in suitable containers of dark glass optionally disposed in a box wherein each container is separately packaged, as well as the other characteristic of the composition of the invention, assures a full stability ~~to~~ of the product as demonstrated by the tests which have been carried out.

Moreover, it has been observed that the pH adjustment of the injectable solution between 7.0 and 7.5, ~~allows for the bringing about of~~ brings about, not only a useful increment of osmolarity towards that degree of hyperosmosis which better than

a slight hypo-osmosis adapts itself to a good tolerability of the injectable solution, but also an ulterior ~~increment~~ improvement in the stability of the darkening solution and ~~to~~ in the turbidity whether in tests of thermic accelerated stability or in exposure to light.

For the adjustment of the pH and consequently of the osmolarity of the 2-arylpropionic acid salts, mixtures ~~have been used~~ of $C_3$-$C_5$ hydroxy di- and tri-carboxylic acids and the alkaline and alkaline earth salts thereof chosen in the group consisting of the tartronic, malic, tartaric and citric acids have been used. Particularly preferred is the use of citric acid combined with ~~the~~ sodium hydroxy and/or sodium citrate.

The dark glass containers are preferably borosilicate phials rendered opaque to light radiations having 290 to 450 nm wave lengths.

Hereunder are given some non-limitative examples of some embodiments of the invention.

Example 1

Working sheltered from light, in an atmosphere and under ~~b~~bubbling nitrogen, 37.5 g (c.a.0.195M) of citric acid and 22.5 g (0.5625M) of sodium hydroxide are dissolved in 12 l of sterile, previously de-aerated water for injectable preparations, ~~previously de-aerated~~. To the solution so obtained is added under stirring 1.2 kg (3M) of (R,S)-ketoprofen salt of d,l-lysine ~~controlling~~ to control the pH of the solution and eventually ~~adjusting~~ adjust it to values varying from 7.0 to 7.5 with additions of sodium hydroxide.

After complete dissolution of the salt, the volume of

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the solution is brought to 15 ml with sterile water for injectable preparations, ~~previously de-aerated~~, and stirring is continued for another 15 minutes to ensure the total homogeneity of the solution. Nitrogen is left to bubble in the solution for 15 minutes. Working ~~is kept~~ under pressure and in a nitrogen atmosphere, the solution is filtered through 0.22 micron cartridges, ~~and~~ collected in suitable shielded containers appropriately protected from exposure to the UV light radiations and then run into the machine for filling phials for distribution in 2 ml glass ampoules, which are sealed in a nitrogen atmosphere. After ~~sterilisation~~ sterilization, the single phials are placed in containers which are made to hold one or more phials. If desired, the single phial holders can be protected individually by films which make them opaque to the transmission of light.

Example 2

~~In a similar manner, as~~ An experiment similar to the experiment described in the preceding Example, ~~working~~ is carried out by substituting the d,l-lysine salt of (R,S)-ketoprofen, ~~with the~~ The d,l-lysine salt of (R,S)-naproxen ~~which~~ is prepared from 0.2M of d,l-lysine dissolved in 700 ml of water to which is added, after heating to the boiling point temperature, 0.202M of finely sub-divided (R,S)-naproxen. ~~From the reaction mixture the~~ The salt separates from the reaction mixture by removing the water for distillation.